Thimerosal in Vaccines

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[Mercury in Plasma-Derived Products]

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Introduction

Thimerosal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes. Over the past several years, because of an increasing awareness of the theoretical potential for neurotoxicity of even low levels of organomercurials and because of the increased number of thimerosal containing vaccines that have been added to the infant immunization schedule, concerns about the use of thimerosal in vaccines and other products have been raised. Indeed, because of these concerns, the Food and Drug Administration has worked with, and continues to work with, vaccine manufacturers to reduce or eliminate thimerosal from vaccines.

In the U.S at present, all of the routinely administered pediatric vaccines are being produced in either thimerosal-reduced (less than 1 microgram of thimerosal per dose; less than 0.5 micrograms of mercury per dose) or thimerosal-free presentations; see Table 1. In the following pages, a discussion of preservatives, the use of thimerosal as a preservative, guidelines on exposure to organomercurials (primarily methylmercury), thimerosal toxicity, recent and future FDA actions, and the Institute of Medicine's recent review of thimerosal in vaccines are presented. This narrative on thimerosal contains references to the literature and links to other sites for readers who wish additional information; for quick reference, a number of frequently asked questions (FAQs) and answers are provided.

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Preservatives in Vaccines

To begin, we need to answer two questions-what are preservatives and why are they used in vaccines. For our purposes, preservatives may be defined as compounds that kill or prevent the growth of microorganisms, particularly bacteria and fungi. They are used in vaccines to prevent microbial growth in the event that the vaccine is accidentally contaminated, as might occur with repeated puncture of multi-dose vials. In some cases, preservatives are added during manufacture to prevent microbial growth; with changes in manufacturing technology, however, the need to add preservatives during the manufacturing process has decreased markedly.

The United States Code of Federal Regulations (the CFR) requires, in general, the addition of a preservative to multi-dose vials of vaccines; indeed, worldwide, preservatives are routinely added to multi-dose vials of vaccine. Tragic consequences have followed the use of multi-dose vials that did not contain a preservative and have served as the impetus for this requirement. One particularly telling incident from Australia is described by Sir Graham S. Wilson in his classic book, *The Hazards of Immunization*

> In January 1928, in the early stages of an immunization campaign against diphtheria, Dr. Ewing George Thomson, Medical Officer of Health of Bundaberg, began the injection of children with toxin-antitoxin mixture. The material was taken from an India-rubber-capped bottle containing 10 mL of TAM. On the 17th, 20th, 21, and 24th January, Dr. Thomson injected subcutaneously a total of 21 children without ill effect. On the 27th a further 21 children were injected...Of these children ...eleven died on the 28th and one on the 29th. (Wilson 1967)

This disaster was investigated by a Royal Commission and the final sentence in the summary of their findings reads as follows:

> The consideration of all possible evidence concerning the deaths at Bundeberg points to the injection of living staphylococci as the cause of the fatalities.

From this experience, the Royal Commission recommended that biological products in which the growth of a

pathogenic organism is possible should not be issued in containers for repeated use unless there is a sufficient concentration of antiseptic (preservative) to inhibit bacterial growth.

The U.S. requirement for preservatives in multi-dose vaccines was incorporated into the CFR in January 1968, although many biological products had contained preservatives, including thimerosal, prior to this date. Specifically, the CFR states:

> Products in multi-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Polio-virus Vaccine, Live Oral; viral vaccine labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume (v/v) glycerin. [21 CFR 610.15(a)]

The CFR also requires that the preservative used

> ...[s]hall be sufficiently non-toxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in combination used it shall not denature the specific substance in the product to result in a decrease below the minimal acceptable potency within the dating period when stored at the recommended temperature. [21 CFR 610.15(a)]

Preservatives cannot completely eliminate the risk of contamination of vaccines. The literature contains several reports of bacterial contamination of vaccines despite the presence of a preservative, emphasizing the need for meticulous attention to technique in withdrawing vaccines from multi-dose vials. (Bernier et al 1981; Simon et al. 1993). The need for preservatives in multi-dose vials of vaccines is nonetheless clear. Several preservatives are used in U.S. licensed vaccines, and these are listed in Table 2. It is important to note that the FDA does not license a particular preservative; rather, the product containing that preservative is licensed, with safety and efficacy data generally collected in the context of a license application for a particular product.

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Thimerosal as a Preservative

Thimerosal, which is approximately 50% mercury by weight, has been one of the most widely used preservatives in vaccines. It is metabolized or degraded to ethylmercury and thiosalicylate. Ethylmercury is an organomercurial that should be distinguished from methylmercury, a related substance that has been the focus of considerable study (see "Guidelines on Exposure to Organomercurials" and "Thimerosal Toxicity", below).

At concentrations found in vaccines, thimerosal meets the requirements for a preservative as set forth by the *United States Pharmacopeia*; that is, it kills the specified challenge organisms and is able to prevent the growth of the challenge fungi (U.S. Pharmacopeia 2001). Thimerosal in concentrations of 0.001% (1 part in 100,000) to 0.01% (1 part in 10,000) has been shown to be effective in clearing a broad spectrum of pathogens. A vaccine containing 0.01% thimerosal as a preservative contains 50 micrograms of thimerosal per 0.5 mL dose or approximately 25 micrograms of mercury per 0.5 mL dose.

Prior to its introduction in the 1930's, data were available in several animal species and humans providing evidence for its safety and effectiveness as a preservative (Powell and Jamieson 1931). Since then, thimerosal has been the subject of several studies (see Bibliography) and has a long record of safe and effective use preventing bacterial and fungal contamination of vaccines, with no ill effects established other than minor local reactions at the site of injection.

While the use of mercury-containing preservatives has declined in recent years with the development of new products formulated with alternative or no preservatives, thimerosal has been used in some immune globulin preparations, anti-venins, skin test antigens, and ophthalmic and nasal products, in addition to certain vaccines. Under the FDA Modernization Act of 1997, the FDA compiled a list of regulated products

containing mercury, including those with thimerosal (Federal Register 1999). It is important to note that this list was compiled in 1999; some products listed are no longer manufactured and many products have been reformulated without thimerosal. Updated lists of vaccines and their thimerosal content can be found in Table 1 (routinely recommended pediatric vaccines) and Table 3 (expanded list of vaccines).

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Guidelines on Exposure to Organomercurials

Mercury is an element that is dispersed widely around the earth. Most of the mercury in the water, soil, plants and animals is found as inorganic mercury salts. Mercury accumulates in the aquatic food chain, primarily in the form of the methylmercury, an organomercurial. Organic forms of mercury are more easily absorbed when ingested and are less readily eliminated from the body than are inorganic forms mercury. Humans are exposed to methylmercury primarily from the consumption of seafood (Mahaffey et al. 1997).

Methylmercury is a neurotoxin. The toxicity of methylmercury was first recognized during the late 1950s and early 1960s when industrial discharge of mercury into Minimata Bay, Japan led to the widespread consumption of mercury-contaminated fish (Harada 1995). Epidemics of methylmercury poisoning also occurred in Iraq during the 1970s when seed grain treated with a methylmercury fungicide was accidentally used to make bread (Bakir et al. 1973). During these epidemics, fetuses were found to be more sensitive to the effects of methylmercury than adults. Maternal exposure to high levels of methylmercury resulted in infants exhibiting severe neurologic injury including a condition resembling cerebral palsy, while their mothers showed little or no symptoms. Sensory and motor neurologic dysfunction and developmental delays were observed among some children who were exposed *in utero* to lower levels of methylmercury

More recently, several epidemiological studies have examined the effect of low dose dietary exposure to methylmercury, with inconsistent results. Studies from the Faroe Islands reported that subtle cognitive deficits (e.g., performance on attention, language, and memory tests), detectable by sophisticated neuropsychometric testing, were associated with methylmercury levels previously thought to be safe (Grandjean et al 1997). Studies in the Seychelles, evaluating more global developmental outcomes, did not reveal any correlation between abnormalities and methylmercury levels (Davidson et al. 1998).

Various agencies have developed guidelines for safe exposure to methylmercury, including the U.S. Environmental Protection Agency (Mahaffey et al. 1997), U.S. Agency for Toxic Substances and Disease Registry (ATSDR 1999), the FDA (Federal Register 1979)[1], and the World Health Organization (WHO 1996). These exposure levels range from 0.1 µg/kg body weight/day (EPA) to 0.47 µg/kg body weight/day (WHO)[2]. The range of recommendations is due to varying safety margins, differing emphasis placed on various sources of data, the different missions of the agencies and the population that the guideline is intended to protect. All guidelines, however, fall within the same order of magnitude. While these guidelines may be used as screening tools in risk assessment to evaluate the "safety" of mercury exposures, they are not meant to be bright lines above which toxicity will occur. However, as exposure levels increase in multiples of these guidelines, there is increasing concern on the part of the public health community that adverse health consequences may occur (Mahaffey 1999).

To address the issue of conflicting methylmercury exposure guidelines, Congress asked the National Academy of Sciences to study the toxicological effects of methylmercury and provide recommendations on the establishment of a scientifically appropriate methylmercury reference dose (RfD) (National Research Council 2000; http://www.nap.edu/catalog/9899.html). Their report concluded that the EPA's current reference dose, the RfD, for methylmercury, 0.1 µg/kg/day is a scientifically justifiable level for the protection of human health. The FDA is considering this and other data relevant to its exposure guideline for methylmercury.

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Thimerosal Toxicity

The various mercury guidelines are based on epidemiological and laboratory studies of methyl mercury, whereas thimerosal is a derivative of ethyl mercury. Because they are different chemical entities - ethyl- versus methylmercury - different toxicological profiles are expected. There is, therefore, an uncertainty that arises in applying the methylmercury-based guidelines to thimerosal. Lacking definitive data on the comparative toxicities of ethyl- versus methylmercury, FDA considered ethyl- and methyl-mercury as equivalent in its risk evaluation. There are some data and studies bearing directly on thimerosal toxicity and these are summarized in this Section.

Allergic responses to thimerosal are described in the clinical literature, with these responses manifesting themselves primarily in the form of delayed-type local hypersensitivity reactions, including redness and swelling at the injection site (Cox and Forsyth 1988; Grabenstein 1996). Such reactions are usually mild and last only a few days. Some authors postulate that the thiosalicylate component is the major determinant of allergic reactions (Goncalo et al. 1996). In a clinical setting, however, it is usually not possible to determine whether local reactions are caused by thimerosal or other vaccine components.

The earliest published report of thimerosal use in humans was published in 1931 (Powell and Jamieson 1931). In this report, 22 individuals received 1% solution of thimerosal intravenously for unspecified therapeutic reasons. Subjects received up to 26 milligrams thimerosal/kg (1 milligrams equals 1,000 micrograms) with no reported toxic effects, although 2 subjects demonstrated phlebitis or sloughing of skin after local infiltration. Of note, this study was not specifically designed to examine toxicity; 7 of 22 subjects were observed for only one day, the specific clinical assessments were not described, and no laboratory studies were reported.

Several cases of acute mercury poisoning from thimerosal-containing products were found in the medical literature with total doses of thimerosal ranging from approximately 3 mg/kg to several hundred mg/kg. These reports included the administration of immune globulin (gamma globulin) (Matheson et al. 1980) and hepatitis B immune globulin (Lowell et al. 1996), choramphenicol formulated with 1000 times the proper dose of thimerosal as a preservative (Axton 1972), thimerosal ear irrigation in a child with tympanostomy tubes (Rohyans et al. 1994), thimerosal treatment of omphaloceles in infants (Fagan et al. 1977), and a suicide attempt with thimerosal (Pfab et al. 1996). These studies reported local necrosis, acute hemolysis, disseminated intravascular coagulation, acute renal tubular necrosis, and central nervous system injury including obtundation, coma, and death. IOM

Several animal studies have evaluated the toxicity of thimerosal. In 1931 Powell and Jamieson reported acute toxicity studies in several animal species. Maximum tolerated doses not associated with death of the animals were 20 mg thimerosal/kg (rabbits) and 45 mg/kg (rats). Blair evaluated the administration of thimerosal intranasally for 190 days and observed no histopathological changes in the brain or kidney (Blair et al. 1975). Magos et al. directly compared the toxicity of ethyl- versus methylmercury in adult male and female rats administered 5 daily doses of equimolar concentrations of ethyl- or methylmercury by gavage (Magos *et al* 1985). Magos concluded that ethylmercury, the mercury derivative found in thimerosal, is less neurotoxic than methylmercury, the mercury derivative for which the various guidelines are based.

One final piece of data regarding thimerosal is worth noting. At the initial National Vaccine Advisory Committee-sponsored meeting of thimerosal in 1999, concerns were expressed that infants may lack the ability to eliminate mercury. At the recent IOM meeting in Boston, data from NIAID-sponsored studies were presented that showed that mercury was excreted by infants into stools.

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Recent and Future FDA Action

FDA has been actively addressing the issue of thimerosal as a preservative in vaccines. Under the FDA Modernization Act (FDAMA) of 1997, the FDA conducted a comprehensive review of the use of thimerosal in childhood vaccines. Conducted in 1999, this review found no evidence of harm from the use of thimerosal as

a vaccine preservative, other than local hypersensitivity reactions (Ball et al. 2001).

As part of the FDAMA review, the FDA evaluated the amount of mercury an infant might receive in the form of ethylmercury from vaccines under the U.S. recommended childhood immunization schedule and compared these levels with existing guidelines for exposure to methylmercury, as there are no existing guidelines for ethylmercury, the metabolite of thimerosal. At the time of this review in 1999, the maximum cumulative exposure to mercury from vaccines in the recommended childhood immunization schedule was within acceptable limits for the methylmercury exposure guidelines set by FDA, ATSDR, and WHO. However, depending on the vaccine formulations used and the weight of the infant, some infants could have been exposed to cumulative levels of mercury during the first six months of life that exceeded EPA recommended guidelines for safe intake of methylmercury.

As a precautionary measure, the Public Health Service (including the FDA, National Institutes of Health (NIH), Center for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA) and the American Academy of Pediatrics issued two Joint Statements, urging vaccine manufacturers to reduce or eliminate thimerosal in vaccines as soon as possible (CDC 1999) and (CDC 2000). The U.S. Public Health Service agencies have collaborated with various investigators to initiate further studies to better understand any possible health effects from exposure to thimerosal in vaccines.

Available data has been reviewed in several public forums including the Workshop on Thimerosal held in Bethesda in August 1999 and sponsored by the National Vaccine Advisory Committee, two meetings of the Advisory Committee on Immunization Practices of the CDC, held in October 1999 and June 2000, and the Institute of Medicine's Immunization Safety Review Committee in July 2001. Through its Vaccine Safety Datalink, the CDC has examined the incidence of autism as a function of the amount of thimerosal a child received from vaccines. Preliminary results indicated no change in autism rates relative to the amount of thimerosal a child received during the first six months of life (from 0 micrograms to greater than 160 micrograms). A weak association was found with thimerosal intake and certain neurodevelopmental disorders (such as attention deficit hyperactivity disorder) in one study, but was not found in a subsequent study. Additional studies are planned in these areas.

Much progress has been made to date in removing or reducing thimerosal in vaccines. New pediatric formulations of hepatitis B vaccines have been licensed by the FDA, Recombivax-HB (Merck, thimerosal free) in August 1999 and Engerix-B (Glaxo SmithKline, trace thimerosal) in March 2000. In March 2001 the FDA approved a second DTaP vaccine formulated without thimerosal as a preservative (Aventis-Pasteur's Tripedia, trace thimerosal). These changes have been accomplished by reformulating products in single dose vials that do not contain a preservative. At present, all routinely recommended vaccines manufactured for administration to U.S. infants are either thimerosal-free or contain only trace amounts of thimerosal (less than 0.5 micrograms mercury per 0.5 mL dose); see Table 1. A more extensive tabulation of vaccines and thimerosal content may be found in Table 3.

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The Safety Review of Thimerosal-containing Vaccines and Neurodevelopmental Disorders Conducted by the Institute of Medicine

This past year, the Institute of Medicine convened a committee (the Immunization Safety Review Committee) to review selected issues related to immunization safety. [For more information regarding this committee, their charge, and their reports, see the IOM web site, www.iom.edu/imsafety] The IOM has, to date, completed reviews in two areas. The first review by this committee focused on a potential link between autism and the combined mumps, measles, and rubella vaccine. The second review focused on a potential relationship between thimerosal use in vaccines and neurodevelopmental disorders (IOM 2001). This latter issue was brought to the fore primarily as the result of the hypothesis, formulated by S. Bernard and others from Cure Autism Now, that autism is a novel form of mercury poisoning (Bernard et al. 2001); this hypothesis, linking autism to mercury, was based on a comprehensive review of the scientific literature on mercury toxicity.

In its report of October 1, 2001, the IOM's Immunization Safety Review Committee concluded that the evidence is inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. Thus, while the available scientific data do not establish that these neurodevelopmental disorders are caused by thimerosal, at the same time, they do not establish that these neurodevelopmental disorders are not caused by thimerosal. Additional studies are needed to establish or reject a causal relationship. The Committee did conclude that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was biologically plausible.

The Committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible." Furthermore, in this regard, the Committee urged that "full consideration be given to removing thimerosal from any biological product to which infants, children, and pregnant women are exposed."

The FDA is continuing its efforts to reduce the exposure of infants, children, and pregnant women to mercury from all sources. Discussions with the manufacturers of influenza virus vaccines (which are routinely recommended for pregnant women) regarding thimerosal-reduced and thimerosal-free presentations are ongoing. Discussions are also underway with regard to other vaccines, in particular, the diphtheria and tetanus vaccines and one manufacturer's adolescent/adult formulation of the hepatitis B vaccine (a second manufacturer's hepatitis B vaccine is formulated without thimerosal as a preservative for both the pediatric and adult presentations.) In addition, all immune globulin preparations including hepatitis B immune globulin, and Rho(D) immune globulin preparations are manufactured without thimerosal. For additional information on the issue of thimerosal in vaccines, see Frequently Asked Questions (FAQs).

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Tables

Table 1. Thimerosal and Routine Pediatric Vaccines

Vaccine	Tradename (Manufacturer)*	Thimerosal Status
DTaP	Infanrix (GSK)	Free
	Tripedia (AP)	Trace** (single dose)
Pneumococcal conjugate	Prevnar (WL)	Free
Inactivated Poliovirus	IPOL (AP)	Free
Varicella (chicken pox)	Varivax (M)	Free
Mumps, measles, and rubella	M-M-R-II (M)	Free
Hepatitis B	Recombivax HB (M)	Free
	Engerix B (GSK)	Trace**
Haemophilus influenzae type b conjugate (Hib)	ActHIB (AP)/OmniHIB (GSK)	Free
	PedvaxHIB (M)	Free

	HibTITER (WL)	Free (single dose vials)
Hib/Hepatitis B combination	Comvax (M)	Free

*Manufacturer abbreviations:
GSK = GlaxoSmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck.

**Less than 1 microgram thimerosal per 0.5 mL dose (equivalent to less than 0.5 microgram of mercury per 0.5 mL dose.)

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Table 2: Preservatives Used in U.S. Licensed Vaccines-- 2001

Preservative	**Vaccine Examples (Tradename; Manufacturer*)**
Thimerosal	DT Td (several) TT (several) Influenza (several) Pneumococcal Polysaccharide (Pnu-Imune 23; WL)
2-phenoxyethanol and formaldehyde	IPV (IPOL; AP)
Phenol	Typhoid Vi Polysaccharide (Typhim Vi; AP) Pneumococcal Polysaccharide (Pneumovax 23; M)
Benzethonium chloride (Phemerol)	Anthrax (B)
2-phenoxyethanol	DTaP (Infanrix; GSK) Hepatitis A (Havrix; GSK) Hepatitis A/Hepatitis B (Twinrix; GSK) Lyme (Lymerix; GSK) [Labeled bacteriostatic agent]

*Manufacturer abbreviations:
GSK = Glaxo SmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck; B=Bioport.

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Table 3: Thimerosal and Expanded List of Vaccines

Thimerosal Content in Some Currently Manufactured U.S. Licensed Vaccines					

Vaccine	Trade Name	Manufacturer	Thimerosal Concentration[1]	Mercury
Anthrax	Anthrax vaccine	BioPort Corporation	0	0
DTaP	Tripedia[2]	Aventis Pasteur	<0.0002% (single dose)	<0.5µg/dose
	Infanrix	GlaxoSmithKline	0	0
DT	All Products		0.01%	25µg/dose
Td	All Products	Mass Public Health	0.003%	25µg/dose
		All other manufacturers	0.01%	
TT	All Products		0.01%	25µg/dose
Hib	ActHIB/OmniHIB[3]	Aventis Pasteur	0	0
	HibTITER (Single dose)	Wyeth-Lederle	0	0
	PedvaxHIB liquid	Merck	0	0
Hib/HepB	COMVAX[4]	Merck	0	0
Hepatitis B[5]	Engerix-B	GlaxoSmithKline	<0.0002%	<0.5µg/dose
	Recombivax HB	Merck	0	0
Hepatitis A	Havrix	GlaxoSmithKline	0	0
	Vaqta	Merck	0	0
IPV	IPOL	Aventis Pasteur	0	0
	Poliovax	Aventis Pasteur	0	0
Influenza[6]	All	Aventis Pasteur, Evans, Wyeth-Lederle	0.01%	25 µg/0.5 mL dose (12.5 µg/0.25 mL dose)
Japanese Encephalitis[7]	JE-VAX	BIKEN	0.007%	35 µg/1.0mL dose (17.5 µg/0.5 mL dose
MMR	MMR-II	Merck	0	0
Meningococcal	Menomune A, C, AC and A/C/Y/W-135	Aventis Pasteur	0.01% (multidose) 0 (single dose)	25 µg/dose
Pneumococcal	Prevnar (Pneumo Conjugate)	Lederle Laboratories	0	0
	Pneumovax 23	Merck	0	0
	Pnu-Imune 23	Wyeth-Lederle	0.01%	25 µg/dose
Rabies	IMOVAX	Aventis Pasteur	0	0
	Rabavert	Chiron	0	0

Typhoid Fever	Typhim Vi	Aventis Pasteur	0	0
	Typhoid Ty21a	Swiss Serum and Vaccine Institute	0	0
Varicella	Varivax	Merck	0	0
Yellow Fever	Y-F-Vax	Aventis Pasteur	0	0

Table Footnotes

1. Thimerosal is 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50 µg of Hg per 1 ml dose or 25 µg of Hg per 0.5 ml dose.
2. Aventis Pasteur's Tripedia may be used to reconstitute ActHib to form TriHIBit. TriHIBit is indicated for use in children 15 to 18 months of age.
3. OmniHIB is manufactured by Aventis Pasteur but distributed by GlaxoSmithKline.
4. COMVAX is not licensed for use under 6 weeks of age because of decreased response to the Hib component.
5. Merck's Hepatitis B vaccine for adults still contains thimerosal as a preservative.
6. Children under 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL (12.5 µg mercury/dose.)
7. JE-VAX is manufactured by BIKEN and distributed by Aventis Pasteur. Children 1 to 3 years of age receive a half-dose of vaccine, i.e., 0.5 mL (17.5 µg mercury/dose).

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[1] FDA's guideline is based in part on a maximum tolerable daily intake of 30 mg/day of methylmercury from the diet; for purposes of comparison this would translate to approximately 0.43 micrograms/kg/day for a 70 kg adult. The FDA recommends that pregnant women, women of childbearing age who may become pregnant, nursing mothers and young children do not consume certain kinds of fish that may contain high levels of methylmercury (i.e., shark, swordfish, king mackerel, and tilefish); see http://www.cfsan.fda.gov/~lrd/tphgfish.html

[2] The WHO guideline is expressed as 3.3 mg/kg/ week and has been converted to a daily dose for purposes of comparison.

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